REMARKS

Claims 20, 21, 23-28 and 30-72 are currently pending. Claims 20, 21, 23-28, 30-72 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Claims 20, 21, 30, 33, 38, 43, 54, and 66 stand rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness.

Applicants greatly appreciate the telephonic interview granted by Examiner A. Owens to Applicants' representative, Thomas S. Kim, on June 15, 2005. Although no specific conclusion was memorialized, Examiner Owens and Mr. Kim discussed various measures to achieve the allowance of claims in the above-identified application, which the present amendments and arguments attempt to follow.

Amendments

Claim 38 has been amended, as suggested by the Examiner, to remove a typographical error and to more clearly express aspects of the present invention.

New claims 73-80 are hereby added. The claims are supported by the specification. Furthermore, the claims are representative of the pending claims – independent claims 73, 75, and 77 track claims 20, 30, and 38, respectively, but further include the limitation, with respect to the second antiretroviral compound, as provided in claim 25, for example. The new claims, claims 74, 76, and 78-80, depend from these independent claims and include further limitations.

Applicants submit that no new matter has been introduced by the present amendments and are fully supported by the specification and claims, as originally filed.

The Rejections Based on Alleged Lack of Enablement Should be Withdrawn

Claims 20, 21, 23-28, 30-72 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement due to the breadth and operability. Applicants traverse the rejection and submit that the claimed invention is fully enabled.

Enablement under 35 U.S.C. § 112, first paragraph, requires that an applicant provide sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention, which is recognized as not requiring "undue experimentation" on the part of one of ordinary skill. MPEP § 2164.01 further provides that "[t]he fact that **experimentation may be complex** does not necessarily make it undue, if the art typically engages in such experimentation." *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Office Has Failed to Meet Burden

The Applicants point to Section 2164.04 of the M.P.E.P. that states the required burden for a rejection based on lack of enablement. In particular, the section provides:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. . . . 'it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.'

Applicants submit that, with respect to the claims directed to compositions (claims 20, 21, 23-28, 73, and 74) and the claims directed to kits (claims 30-37, 75, and 76), the specification does teach the manner and process to make and use the claimed invention and the Office has failed to provide the requisite explanations for doubting the truth or accuracy of the statements found in Applicants' specification.

Compositions

Claims 20, 21, 23-28, 73, and 74 are directed to compositions that combine (a) Applicants' antiretroviral compound with the specific formula (I), with (b) a second

antiretroviral compound and (c) a pharmaceutically tolerable excipient. Applicants teach how to make and use (a) – compounds with the specific formula (I). The synthesis of an embodiment, hexahydrofuro[2,3-b]furan-3-yl-N-{3-[1,3-benzodioxol-5-ylsufonyl)(isobutyl)amino]-1-benzyl-2-hydroxypropyl}carbamate, or compound 13, (formula (I) compound) is shown, for example, on pages 12-15 of the specification, wherein the citations made herein are to PCT Publication No. WO 01/2540. Furthermore, the specification shows use of formula (I) compound to prevent retroviral infection in a cell on page 16, line 16 – page 17, line 5. The other components of the composition, (b) and (c), are well known to one of ordinary skill. For example, a plethora of antiretroviral compounds are known to those of ordinary skill and the second antiretroviral compound (b) only requires a compound known to have antiretroviral activity. In contrast to the Office's allegation that "one of ordinary skill in the art would have to pick and choose a specific compound from among the class of compounds, combine them with formula I and then determine if said composition has antiretroviral activity," Applicants clarify that the composition claims only require a composition combining the specific compound 13 (and derivatives including compound 14 on page 6 of specification) with a **known** antiretroviral compound along with a **known** pharmaceutically tolerable excipient.

In addition, the specification, along with general knowledge in the art, fully teaches to one of ordinary skill in the art how to make and use the combination of (a), (b), and (c). The pharmaceutical combinations are described on page 6, line 20 – page 7, line 3, and a list of second antiretrovirals are provided on page 8, lines 5-22 of the specification. Knowledge in the art provides that retroviruses, such as HIV, quickly mutate, developing drug resistance to known anti-retroviral drugs, *e.g.,* see page 17, lines 20-23 of the specification. The teachings provided in the specification instruct a person of ordinary skill how to combine antiretroviral compounds, including formula (I) compounds, to overcome the phenomena of drug resistance. On page 17, line 28, the specification provides results showing activity of the formula (I) compound on retroviral strains resistant to known retroviral protease inhibitors saquinavir, ritonavir, indinavir, nelfinavir, and amprenavir. Applicants submit, therefore, that a person of ordinary skill in the art, based on the teachings provided in the specification, combined with the knowledge in the art, would be equipped to make and use the claimed combinations without any undue experimentation.

Kits

Claims 30-37, 75 and 76 are directed to kits comprising the claimed compositions, which include any **known** antiretroviral compound in combination with the provided **compounds of formula I**, and instructions for administering the combination for "preventing or treating viral infections." Applicants submit that claims 30-37, 75 and 76 do not claim kits to all combinations that "prevent or treat retroviral infections" but only those kits with compositions comprising the antiretroviral compound of formula (I) and select derivatives.

Applicants submit that, the specification does teach the manner and process to make and use the claimed compositions and kits and the Office has failed to provide the requisite reasons as to why the teachings should be doubted for its objective truth or accuracy. As such, the Office has failed to meet its burden of proof. Applicants submit that the specification clearly shows that the claimed compositions and kits are taught and these teachings enable one of ordinary skill to make and use the same. Therefore, the rejection with respect to the composition and kit claims should be withdrawn.

The Specification Enables a Skilled Artisan to Practice the Claimed Method

Claims 38-72, and 77-80 are directed to the methods employing the claimed compositions and all their limitations. The method claims have been amended to more clearly define the invention, as represented by amended claim 38 and new claim 77 (claims 39-50 depend from claim 38, and claims 78 and 79 depend from claim 77), which are directed to a "method of **treating an infection associated with a retrovirus** in a mammal." Additionally, claims 50 and 61, and the claims that depend therefore (claims 51-60 and 62-72, respectively), are directed to a "method of inhibiting retroviral replication" and a "method of inhibiting a protease of a retrovirus," respectively, and these claims are in no way directed to treating all diseases associated with retrovirus infection. The method claims are simply directed to treating retroviral infections and, more particularly, an aspect of the infection pathway, *e.g.,* retroviral protease activity.

Inapposite to the present method claims, the Office suggests that Applicants are "claiming all such infections or diseases know [sic] to [be] associated with retrovirus

infection and such as may be determined to be associated in the future and such is wholly inoperable." The Applicants submit that the breadth of the compositions underlying the claimed methods are nowhere near the breadth the Office suggests. The specification teaches use of claimed combinations for treating the underlying retroviral infection. This is supported by the effectiveness of antiretroviral compounds of formula (I) as shown in the cellular assays provided in the specification, pg 16, ln 16 – pg 19, ln 16. In addition, the effectiveness of formula (I) compounds are shown with respect to mutant retroviruses that are resistant to known retroviral protease inhibitors, including saquinavir and ritonavir for example on page 17, lines 20 – 35 and Table 1 of the specification. The Applicants are simply claiming the combination of another known antiretroviral compound to further add to the efficacy of the compounds of formula (I), in part, to avoid resistance due to rapid mutations in retroviruses.

It is widely known that retroviruses, such as HIV, quickly mutate and, because of this, combinations of antiretroviral compounds are typically effective treatments. In support, references such as Principal Health News, www.principalhealthnews.com/topic/retrodrugs, recognize that because of the high rate of mutation, "treatment with drug combinations appears to produce a durable response." See Appendix A. Also, The Hopkins HIV Report focuses on the wide attention placed on dual protease inhibitor therapy, www.aegis.com/pubs/jhopkins/1998/JH980501.html. See Appendix B. These references represent only a small sampling of the numerous literatures available discussing the paradigm of multiple-therapeutics for effective treatment of retroviral infections.

Additionally, regarding the "ester, prodrug or metabolite of the compound of formula I," Applicants submit that such forms of the compounds of formula I are clearly expressed and taught in the present specification. The ester, prodrug or metabolites are described as derivatives of compounds of formula I such that the "resulting biotransformation product of the derivatives is the active drug as defined in the compounds of formula (I)." Pg 2, ln 32 – Pg 3, ln 3 of the specification. Furthermore, the specification also cites to the known art of biotransformation of drugs on pg 3, lines 3-7, Goodman and Gilman, The Pharmacological Basis of Therapeutics, 8th Ed., McGraw-Hill, Int. Ed. 1992, p 13-15, along with several PCT publications: WO 99/33795, WO 99/33815, WO 99/33793, and WO 99/33792. In light of

the teachings of ester, prodrug and metabolite derivatives of formula (I) compounds provided in the specification, Applicants respectfully request the withdrawal of this rejection.

Applicants submit that the teachings provided in the present application enable one of ordinary skill to make and use the claimed compositions, kits and methods without undue experimentation, and the enablement rejection should be withdrawn.

Rejection under 35 USC § 112, 2nd Paragraph for Indefiniteness

Claims 20, 21, 30, 33, 38, 43, 54, and 66 stand rejected under section 112, second paragraph for alleged indefiniteness because of use of the term "prodrug" and, with respect to claim 38, "of treating or treating."

Applicants have amended claim 38 to remove a typographical error and to more clearly express aspects of the present invention.

Furthermore, Applicants traverse the rejection based on "prodrug" because, as explained, above, the prodrug derivatives of the compounds of formula I have been expressed and taught on pg 2, ln 32 – pg 3, ln 11 of the specification.

Accordingly, this rejection no longer applies and Applicants respectfully request its withdrawal.

Conclusion

In light of the foregoing amendments and remarks, the Applicants respectfully submit that all claims are in condition for allowance and solicit an early indication to that effect. The Examiner is invited to contact the undersigned at the telephone number indicated below in order to discuss any remaining concerns in an effort to expedite allowance.

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Thomas S. Kim
Registration No. 51,009

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439